

Neuropathic Pain in Fabry Disease



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Abstract

Fabry Disease [FD] is an X-linkedly so somal storage disease caused by the mutations in the GLA gene coding for the lysosomal enzyme α -galactosidase in chromosome Xq 22.1. The disease leads to accumulation of neutral sphingolipids in tissues. About 80% of Fabry patients [FP] suffer from a painful neuropathy that usually begins in the first two decades. About 80% of FP suffer from a painful neuropathy. Enzyme replacement therapies with recombinant human α -galactosidase A is reported to improve small fiber neuropathy and neuropathic pain after 18-23 months of therapy. Enzyme replacement therapies has positive effects on neuropathic pain in FD. Quality of life was decreased in Fabry males in the domains of physical functioning and bodily pain and of general health perception in females. Carbamazepine alone or in combination with pregabalin is recommended as first line treatment in neuropathic pain of FD. Neuropathic pain diagnosis in Fabry patients deserves no reattention especially in adolescents and women with increasing diagnostic skills. We believe neuropathic pain of Fabry Disease will be diagnosed more frequently.

Keywords: Fabry disease, Enzyme replacement therapy, Neuropathic pain, Pregabalin

Abbreviations: ERT: Enzyme Replacement Therapy; FD: Fabry Disease; FP: Fabry Patients; MSI: Mainz Severity Score Index; NP: Neuropathic pain

Introduction

Fabry Disease [FD] is an X-linkedly so somal storage disease caused by the mutations in the GLA gene coding for the lysosomal enzyme α -galactosidase in chromosome Xq22.1 [1]. The disease leads to accumulation of neutral sphingolipids in tissues. Undegraded glycosphingo lipids, especially globotriaosylceramide Gb3, accumulate mainly in the vascular endothelium and peripheral nervous system [1,2]. Neuropathic pain [NP] episodes are common both in childhood and adulthood. Neuropathic pain develops as a result of lesions or disease affecting the somato sensory nervous system either in the periphery or centrally.

Pain crises with sudden sharp pain in digits may be triggered by changes in skin temperature through cold, heat exposure or fever during infections [3]. Despite the cardinal presenting symptoms in childhood of acroparesthesias, pain crises, and angio keratomas, FD is often misdiagnosed or overlooked [4]. Clinically, small fiber dysfunction contributes to recurrent episodes of burning and lancinating pain and paresthesias in the distal extremities. Such episodes can be typically triggered by changes of the environmental temperature, particularly by warming [5].

About 80% of Fabry patients [FP] suffer from a painful neuropathy that usually begins in the first two decades [6]. The degree of the painful neuropathy can be characterized by the use of standardized pain scales [7]. Female heterozygote carriers of the genetic defect might also develop symptoms of the disease. Neuropathic pain of the female carriers corresponds to the pain reported by male patients and usually also occurs in the first two decades [8].

Discussion

The most significant emphasis on Fabry neuropathic pain is on childhood form of the disease and adult FD with neuropathic pain are usually under diagnosed especially in countries where awareness of FD is low. Although adulthood is known to reduce the burden of pain in FP, there are not any studies comparing the severity of pain in childhood with the severity in adulthood.

Chronic burning peripheral pain, attacks of acute excruciating peripheral pain and autonomic dysfunction should prompt the clinician to consider FD and to perform appropriate tests [7]. The burden of the progressive neurologic disease should be assessed early because neurologic disability in FD increases with age, both in males and females.

The early neurologic manifestations of FD are initially often subtle and affected children are frequently misdiagnosed. Fatigue and emotional disturbances co-occur with Fabry-related pain. While some patients report that their physicians understand them, others feel their physicians do not believe them and/or think they exaggerate the pain [9]. In a report of an expert panel in 2011, the authors suggested that a thorough physical examination [e.g., angiokeratomas, corneal opacities] and simple non-invasive sensory perception tests could provide clues to the diagnosis of FD [7].

The burden of disease in women can be substantial. For example the Mainz Severity Score Index [MSSI] shows that men and women experience a similar impact from FD [8,9,10] and health related quality of life is similarly reduced in women and men with FD [11]. Without treatment, lifespan is typically reduced by 15 years in women with FD.

According to a cohort study of 36 women for 4 years, Brief Pain Inventory scores of the patients was reduced by ERT [$p=0.001$] and remained reduced through four years [1,12]. It was concluded that long term agalsidase alpha was effective and well tolerated in women with FD.

Enzymereplacementtherapies with recombinant human α -galactosidase A is reported to improve small fiber neuropathy and neuropathic pain after 18-23 months of therapy. The authors stated that this effect resulted from glycol sphingo lipid clearing from perineural cells, axons and Schwann cells or from blood vessels supplying the nerves. Enzymereplacementtherapies has positive effects on neuropathic pain in FD according to Schiffmann et al. [13]. They reported that FP participating in ERT could reduce their regular pain medications [14]. Dutsch et al. [5] performed quantitative sensory testing in FP under ERT [5].

Quantitative sensory tests are time consuming and are not widely used and popular among physicians who deal with FP most commonly. On the other hand, simple pain questionnaires targeting to diagnose the severity of neuropathic pain may be more user-friendly and practical.

Neuropathic pain affects quality of life in both men and women with FD [11,15]. Neuropathic pain interferes with both activities of daily living and quality of sleep at night, thus depression is often seen in these patients. Pain affects major daily functions of life.

Little is known on the impact of growing up with FD on psychosocial development [16]. Quality of life was decreased in Fabry males in the domains of physical functioning and bodily pain and of general health perception in females according to a study by Bouwman et al. [16]. They used Course of Life Questionnaire and the Short Form Health Survey [SF-36] in this study.

A validated disease severity scoring system for FD was suggested by Gianini et al. in 2010. Their study shows that

the Fabry DS3 correlates highly with the clinical assessment by FD experts. It is obvious that validations of FDS3 should be performed in other countries where English is not the native language and thus validation studies will be needed and this may take time [17].

There is not a randomized controlled trial of an analgesic for the treatment of painful peripheral neuropathy in FD, only some empiric use of drugs has been reported [7]. Carbamazepine alone or in combination with pregabalin [rather than gabapentin] is recommended as first line treatment in neuropathic pain of FD. [18,19,20]. Antidepressants, particularly dual reuptake inhibitors of both serotonin and norepinephrine [SNRIs, venlafaxine, duloxetine] are also viable options although, tricyclic antidepressants have potential concomitant and difficult side-effects in FP [e.g. accentuation of autonomic instability] [7,18,19,20].

Although experts of pain recommend pain scales, they have not gained popularity among clinicians who deal with Fabry disease mostly. One of the reasons for this observation may be the difficulty of usage in the pediatric population. Nevertheless we should not forget that there are adult patients having NP, thus simple diagnostic scales like DN4 may be practical to use in clinical routine. A neuropathy pain assessment scale should be used at the initial assessment and follow up examinations.

Conclusion

Neuropathic pain diagnosis in Fabry patients deserves more attention especially in adolescents and women with increasing diagnostic skills and we believe neuropathic pain of Fabry Disease will be diagnosed more frequently and thus we need more studies involving Fabry neuropathic pain.

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